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TRANSMITTAL LETTER

In re Application of:
MEULEMAN, DIRK et al.

Serial No.: 09/380,695

Filing Date: March 29, 2002

For: USE OF A 7α-METHYL-17α-ETHYNYL-ESTRANE DERIVATIVE FOR THE TREATMENT OF ATHEROSCLEROSIS

Docket: 1997.263 US

Examiner: Wang, S.

Group Art Unit: 1617

CERTIFICATE OF FACSIMILE TRANSMISSION
I hereby certify that the attached correspondence (7 sheets) is being faxed to 571-273-8300 to the Commissioner for Patents

on May 22, 2006

Lynn Brush

Lynn Brush

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

☒ Transmitted herewith find the document(s) related to this application:

1. **TRANSMITTAL LETTER IN DUPLICATE;**
2. **REPLY BRIEF;**
3. **CERTIFICATE OF FACSIMILE**

☐ Applicant hereby petitions for an extension of time under 37 CFR 1.136 of:
☐ One Month ($ 120.00) ☐ Two Months ($ 450.00)
☐ Three Months ($1020.00) ☐ Four Months ($1590.00)

The total fee believed due is **$0.00.** Please charge this amount and any other fees which may be due (including filing fees under 37 CFR 1.16 and processing fees under 37 CFR 1.17) to Deposit Account No. 01-1350. If an extension of time is required but has not been requested above, Applicant hereby petitions for an extension of time sufficient for the attached document(s) to be timely. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Susan Hess

Susan Hess
Attorney for Applicant(s)
Reg. No. 37,350

Akzo Nobel Inc.
Intellectual Property Dept.
7 Livingstone Avenue
Dobbs Ferry, NY 10522-3408
Tel No.: (973) 422-7474

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APPELLANTS' REPLY BRIEF UNDER 37 C.F.R. 41.41

Sir:

Appellants submit this Reply Brief in response to the Examiner's Answer dated March 22, 2006 (Answer) to Appellants' Brief on Appeal.

The appealed claims 1-4 and 6 are directed to a method of inhibiting the atherosclerotic process by administering to a mammal an effective amount of a 7 α-methyl-17α-ethynyl-estrane derivative of a specified general formula.

Claims 1-4 and 6 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Haenggi et al. in view of Berglund. In particular, the Examiner contends that Haenggi et al. teach a method of decreasing lipoprotein (a) [Lp(a)] by administering tibolone to a human and that Haenggi et al. also teach that Lp(a) is a strong independent risk factor for coronary disease (Answer on page 3). The Examiner also contends that Berglund teaches that Lp(a) has been implicated with an increase risk of atherosclerosis (Answer on page 4). According to the Examiner, it would have been prima facie obvious to employ tibolone as a method of inhibiting atherosclerosis since Lp(a) has been indicated to increase risk of atherosclerosis, and lowering the level of Lp(a) would have reasonably expected to inhibit the progress of atherosclerosis (Answer on page 4).

In this Reply Brief, Appellants incorporate by reference the arguments previously made in the Brief on Appeal and in particular address the Examiner's remarks that were made on pages 4-6 of the Answer in response to Appellants' arguments.

On pages 4-5 in the Answer, the Examiner contends that Appellants' arguments pertaining to the Examiner's impermissible use of hindsight analysis are improper. In particular, the Examiner states:

> "It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin 443 F.2d 1392, 170 USPQ 209 (CCPA 1971)." ...It is noted that appellants do not dispute the fact that "a substantial portion of the population of postmenopausal women are suffering atherosclerosis, but argue that Haenggi et al. disclose that Tibolone also decrease the HDL-cholesterol. The arguments are improper. Particularly, the cited prior arts established that Lp(a) is closely associated with atherosclerosis, therefore, decrease of LP(a) would have been reasonably expected to suppress, or inhibit the development of atherosclerosis. Applicants argue that Tibolone decrease HDL-cholesterol, however, fails to establish the relationship of the decrease of HDL-cholesterol and atherosclerosis. Applicants fails to establish a prima facie case that decrease of HDL-cholesterol would have discourage[d] one of ordinary skill in the art from using Tibolone for inhibiting atherosclerosis. Note, Haenggi et al. merely teaches that lowering lipoprotein (a) would counter balance the adverse effect of tibolone on other lipoprotein risk factors. There is no teaching as to the relation of those factors and atherosclerosis. Further, even if it is known that decrease of HDL-cholesterol is associated with atherosclerosis, there is no sufficient evidence to show that the decrease of HDL-cholesterol would out weight the benefit of lowering Lp(a), particularly, in view the fact that Lp(a) has been shown to be a strong independent risk factor for coronary heart disease."

Appellants respectfully disagree with the Examiner's conclusion and reiterate that the Examiner has engaged in the improper use of hindsight reasoning for the reasons set forth below.

With respect to the Examiner's assertion that "appellants do not dispute the fact that a substantial portion of the population of postmenopausal women are suffering atherosclerosis" it is noted that Appellants have disputed this assertion. (Brief on Appeal on page 6). As pointed out by the Appellants, the Examiner acknowledged that Haenggi et al. do not expressly teach that postmenopausal women studied are suffering from atherosclerosis. By the Examiner's own assertion, it is clear that the Examiner has used improper hindsight reasoning. The Examiner's reasoning improperly assumes that the claimed method should be used to treat postmenopausal women suffering from atherosclerosis, then asks the question whether there is any reasons NOT to do so. As the Appellants have previously made clear, there is no teaching or specific suggestion in Haenggi et al. to treat those suffering from atherosclerosis with tibolone.

That the Examiner has engaged in improper hindsight reasoning is further supported by the Examiner's statement that Haenggi et al. merely teach that lowering Lp(a) would counter balance the adverse effect of tibolone on other lipoprotein risk factors.

It is well-established that the teachings of the prior art must be considered in its entirety. While the Examiner can "take into account knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made", it is impermissible for the Examiner to discount specific teachings of Haenggi et al. to support a particular position. While Haenggi et al. indicate that Lp(a) is a strong independent risk factor for coronary heart disease and that tibolone decreased Lp(a), Haenggi et al. on page 648, first column, first paragraph, also indicate that tibolone treatment significantly decreased high density lipoprotein-cholesterol and its major apolipoprotein A-I. Haenggi et al. also indicate on page 648, first column, third paragraph, that while treatment with tibolone did not significant alter total cholesterol, triacylclycerols and low density lipoprotein-cholesterol, apolipoprotein B showed a highly significant increase. Haenggi et al. also indicate on page 648, first column, third paragraph, that elevated serum concentrations of apolipoprotein B are significantly correlated with a higher risk for cardiovascular disease in woman. Further, Haenggi et al. on page 649, second column, state that the possibly beneficial effect of tibolone on reducing liproprotein A serum levels "might counterbalance, at least to some extent, the theoretical adverse effect on the other lipoprotein risk factors, such as the important decrease of high density lipoprotein-cholesterol and the significant increase in apolipoprotein B." [emphasis added by underlining]

Accordingly, Haenggi et al. considered in its entirety, describe 1) the presence of other lipoprotein risk factors such as the decrease in high density lipoprotein-cholesterol and increase in apolipoprotein B, that must be taken into consideration with Lp(a) when assessing the risk of coronary disease, and 2) that there are both positive and negative effects of tibolone on lipoprotein risk factors.

While Berglund indicates that Lp(a) has been found to be an independent risk factor for cardiovascular disease, Berglund also indicates that the number of prospective studies undertaken so far have been relatively few and Lp(a) has not emerged as a significant risk factor in all of these studies (see Berglund, page 48, first paragraph). Berglund further indicates that the issue as to whether Lp(a) levels should be treated is still debated (see Abstract). Accordingly, Berglund as a whole and at most teaches that Lp(a) may be of potential clinical importance as a risk factor.

Thus, Haenggi et al. combined with Berglund, when considered in their entirety, do not teach or specifically suggest the overall strong atheroprotective properties of tibolone. Further, one skilled in the art when considering Haenggi et al. combined with Berglund, in view of the

number of important risk factors associated with coronary disease and the positive and negative effects of tibolone on risk factors for coronary disease, would not have a reasonable expectation that tibolone would have an overall strong inhibitory effect on atherosclerosis.

In the Answer, the Examiner also contends that the non-obvious effects of tibolone treatment on cholesterol accumulation in the vessel wall, fatty streak formation and advanced lesion formation observed in a rabbit model are not commensurate in scope with the presently claimed method. (Answer pages 5-6) Specifically, the Examiner states:

> "The data is based on rabbit, which, applicant admitted, is different from other mammal[s], such as human (Lp(a) is not present, page 6 of the response submitted December 30, 2003). There is no reasonable expectation that such unexpected result would be extrapolated to other mammal[s]. Therefore, the unexpected results are not commensurate with the scope herein claimed."

Appellants respectfully disagree with the Examiner's conclusion and assert that the non-obvious beneficial effects observed in rabbit using tibolone are commensurate in scope with the presently claimed invention.

In contrast to humans, rabbits do not contain Lp(a), however, use of the rabbit model of arteroscierosis showed that tibolone strongly inhibited cholesterol accumulation in the vessel wall, fatty streak formation and advanced lesion formation. The atheroprotective effect of tibolone was stronger in comparison with the atheroprotective effect of estradiol or estradiol decanoate and was independent of Lp(a). Consequently, as indicated in the specification on page 6, first paragraph, when in humans a decrease in Lp(a) plays an additional role in atheroprotection, the strong atheroprotective effect observed in rabbits might even be stronger in humans. In addition, the specification on page 5, last full paragraph, indicates that these effects on the vessel wall were observed in a general accepted, relevant and validated atherosclerosis model in rabbit. [emphasis added] The specification on page 8, second full paragraph, also makes clear that the rabbit model is considered relevant to the human atherosclerotic process, because the cellular events occurring during the development of the atherosclerotic lesions during the atherogeneic diet are similar to those observed in different states of atherosclerotic processes in coronary arteries. The Examiner has not provided any objective evidence to contradict the relevancy of the rabbit model to the human atherosclerotic process. Accordingly, there is a reasonable expectation that the results obtained from the rabbit model of the atherosclerotic process can be extrapolated to mammals such as humans, and thus the beneficial results shown with the rabbit model of the artherosclerotic process are commensurate in scope with the presently claimed method.

In view of the foregoing, Appellants submit that the rejection of claims 1-4 and 6 in this case is in error and should be reversed.

Respectfully submitted,

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